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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,049	11/13/2006	David Morritz De Kretser	PARA003US	5961

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/26/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@convergentlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,049	DE KRETSER ET AL.	
	Examiner	Art Unit	
	MAHER HADDAD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,8-10,13-16,18-22,27-30,61,65 and 68-78* is/are pending in the application.

5a) Of the above claim(s) *1,2,8-10,13-16,18-22,27-30,61,65 and 68-73* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *74-76* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :05/20/2011, 05/20/2011 and 05/27/2011.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 07/08/2011, is acknowledged.

2. Claims 1-2, 8-10, 13-16, 18-22, 27-30, 61, 65 and 68-78 are pending.

3. Newly amended claim 1-2, 10, 18, 19, 30, 61, 65, 68-71 and newly submitted claims 72-73 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant election, filed 3/16/2009, elected airway inflammation as the specific condition, an acute inflammatory response and targeting activin A as the species. The amended claims read on systemic inflammatory response which does not read on the elected airway inflammation and activin A as the target. Original claims 1-2 and dependent claims thereof were generic claims directed to treat/downregulate any condition/inflammatory response (which can be rejected under using any condition), the amended claims are now directed to a particular inflammatory response, i.e., systemic inflammatory response. Systemic inflammatory response is not the elected species. Newly added claims 74-78 recite severe acute respiratory distress syndrome or asthma which read on the elected airway inflammation.

Accordingly, claims 1-2, 10, 18, 19, 30, 61, 65, 68-73 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and MPEP 821.03.

4. Claims 1-2, 8-10, 13-16, 18-22, 27-30, 61, 65, 68-73 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

5. Claims 74-78 are under consideration in the instant application as they read on a method of modulating the inflammatory response/therapeutically and/or prophylactically treating a condition, wherein modulating is downregulation of activin functional activity, achieved by introducing a proteinaceous molecule which functions as an antagonist of the activin expression product, wherein the antagonist is follistatin, and (i) airway inflammation as the specific condition; (ii) an acute inflammatory response; and (iii) targeting activin A.

6. Applicant's IDS, filed 05/20/2011, 05/20/2011 and 05/27/2011, is acknowledged.

7. The following new ground of rejections are necessitated by the amendment submitted 07/08/2011. Applicant's arguments will be addressed as they pertain to the new ground of rejection.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "nonfibrotic inflammatory response" claimed in claim 78 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 07/08/2011 does not point to the specification for the newly added limitations "nonfibrotic inflammatory response" as claimed in claim 78. However, the specification does not provide a clear support of "nonfibrotic inflammatory response". The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 78 is rejected under 35 U.S.C. 102(b) as being anticipated by WO/ 2003/006057 (IDS).

The `057 publication teaches and claims a method of a method for the treatment of disease associated with fibrosis in a vertebrate in need of said treatment, wherein said method comprises administering to said vertebrate, a therapeutically effective amount of at least one activin antagonist (see published claim 24), wherein the disease associated with fibrosis is one of: an inflammatory bowel disease, or a related condition such as ulcerative colitis or Crohn's Disease (nonfibrotic inflammatory response) (see published claim 28). The `057 publication further teaches a method for the treatment of disease associated with fibrosis in a vertebrate in need of said treatment, wherein said method comprises administering to said vertebrate, a therapeutically effective amount of the pharmaceutical composition comprising a activin antagonist such as follistatin, or a fragment(s) or analogue thereof (see published claims 2 and 25), wherein the follistatin is a single chain protein comprising between 288 and 315 amino acids (see published claim 3, wherein the vertebrate is selected from the group consisting of human, non-human primate, mice, cattle, sheep, goats, horses, rabbits, birds, cats and dogs (see published claims 27 and 28). The `057 publication teaches that interstitial lung disease (ILD) referred to as interstitial pulmonary fibrosis or pulmonary fibrosis. The lung is usually damaged in some way, resulting in inflammation in the walls of the air sacs (alveolitis), in the walls of the bronchioles (bronchiolitis) or in the capillaries (vasculitis) (see page 1, lines 20-18).

While the prior art teachings may be silent as to the "the downregulation of the inflammatory response" in claim 78 per se; the method, the product used in the reference method are the same as the claimed method. Therefore the limitation is considered inherent properties.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 07/08/2011, have been fully considered, but have not been found convincing.

Applicant submits the new claim 78 recites specific nonfibrotic inflammatory condition. Applicant characterizes the teachings of `057 publication as directed to specifically to treatment fibrotic disorders.

It is the Examiner's position that the follistatin in the `057 publication is used to treat diseases associated with fibrosis such as an inflammatory bowel disease, or a related condition such as ulcerative colitis or Crohn's Disease (nonfibrotic inflammatory response) (see published claim 28) (a nonfibrotic inflammatory response), but not fibrosis itself.

12. Claims 74-75 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by US 20020192216 as is evidenced by van Eyll et al (Jounal of Cell Science 117(10):2077-2086, 2004).

The `216 publication teaches a method of treating inflammation (see published claims 1 and 11), adult respiratory distress syndrome, chronic obstructive airway disorders such as asthma or emphysema (published claim 29), idiopathic interstitial lung diseases (see published claims 7, 26, 41), multiple sclerosis, rheumatoid arthritis (nonfibrotic inflammatory response (see published claim 9), comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 1), wherein the inhibitor is Follistatin. The `216 publication teaches a method of treating comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 7). Follistatin has been found to inhibit others aspects of BMP activity as well as acting as an activin-binding protein (¶78 and Table 3). van Eyll et al teach that sonic hedgehog (Shh) signaling can be triggered by activin A and inhibited by follistatin (see page 2085 last ¶).

It is noted that the CAFC held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, *consists of the same steps described in a prior art reference*, and the newly discovered results of the known process *directed to the same purpose* are inherent, the process is not patentable.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which follistatin alleviates symptoms of inflammation does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. *In re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The reference teachings anticipate the claimed invention.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 07/08/2011, have been fully considered, but have not been found convincing.

Applicant argues that the `216 publication discloses that follistatin is an inhibitor of an intracellular signaling pathway, but fails to provide an enabling disclosure regarding the use of follistatin to treat any therapeutic indication. Applicant notes that the `216 publication was abandoned after a lengthy prosecution during with the '216 publication was abandoned after a lengthy prosecution during which the Examiner in the case repeatedly rejected the application ('216 publication) as failing to provide a written description. The Examiner noted that the Applicant of the '216 publication disclosed only limited species of antigens recognized by antagonistic antibodies, namely shh, HIP, WIF1 and Dvl, and concluded that the Applicant of the '216 publication was not in possession generally of antagonistic antibodies to the recited signaling pathways or targets of the signaling pathways. No examples or evidence was presented in the '216 publication relating to the efficacy of follistatin to treat any disease, disorder or condition. Applicant contend that the `216 publication is not enabling, at least as far as follistatin is concerned. Further Applicant dispute whether the public would have been in possession of any therapeutic treatment given the disclosure in the `216 publication specifically, the `216 publication teaches administertion of an inhibitor of the Hedgehog signaling pathway to treat a laundry list of diseases listed on ¶149-155.

Applicant further argues that the '216 publication tosses out the mere germ of an idea relating to the treatment of a panoply of diseases, and that one skilled in the art would have been hard pressed to identify follistatin specifically as one of the many disclosed inhibitors of the Hedgehog signaling pathway as a therapeutic agent without undue experimentation. Further, one skilled in the art would have had to perform an enormous amount of experimentation to arrive at systemic inflammatory conditions--or any other specific therapeutic indication for that matter--as a likely therapeutic indication given the laundry list of diseases, disorders, conditions, etc., that are disclosed in the '216 publication. Thus, Applicants respectfully submit that one skilled in the art would have had to perform an undue amount of experimentation to arrive at the working combination of follistatin as a therapeutic agent and systemic inflammatory conditions as a therapeutic indication out of the colossal number of permutations and combinations of

therapeutic agents and therapeutic indications possible upon reading the '216 reference. Indeed, Dr. David de Kretser so states at ¶ 8 of the Declaration of David Morritz de Kretser ("de Kretser Declaration") submitted herewith. In addition, Dr. de Kretser concludes that there is a high likelihood that a therapeutic response may not be achieved even with a vast amount of experimentation. Moreover, as Dr. de Kretser states in his Declaration at ¶¶4-6, a review of the published literature does not support the information disclosed in the specification of the '216 publication. First, several studies indicate that inhibition of hedgehog signaling actually promotes inflammation, particularly in the gut (discussed in the de Kretser Declaration at ¶4). Second, in animal models of lung disease, hedgehog signaling appears to be upregulated in fibrotic processes, but not in nonfibrotic inflammatory processes (discussed in the de Kretser Declaration at ¶5). Further, the complexity of the hedgehog signaling pathway and the regulation of activins A and B in different systems leads to unpredictability of the effect of activin or follistatin on Shh signaling (discussed in the de Kretser Declaration at ¶6). Dr. de Kretser concludes at ¶7 that the disclosure of the '216 publication--drawn to inhibiting a hedgehog signaling pathway to treat a host of disparate and complex human diseases--is overly simplistic and not supported by studies reported in the literature.

However, Applicant's arguments are inconsistent with the instant disclosure as filed, particularly the description of invention which describes using follistatin to treat a laundry list of diseases listed on ([0079], [0082], [0083], [0088]- [0093], [0107]- [0111], [0172]- [0176], [0191]- [0195] and [0211]- [0215]. Additionally, applicant is reminded that the no working examples present in the instant specification to demonstrate enablement comprise the administrations of follistatin to treat severe acute respiratory distress syndrome or asthma to mice or humans. As such, applicant appears to argue for a double standard, holding the teachings of the prior art to a higher level of enablement that what is found in the instant specification. The courts have examined this issue, and in cases such as *Rasmusson v. SmithKlein Beecham Corp.,* 75 USPQ2d 1297 (CAFC 2005), it is stated:

> "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. In *In re Hafner*, 410 F.2d 1403 [161 USPQ 783] (CCPA 1969), the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim." *Id.* at 1405; *see Schoenwald*, 964 F.2d at 1124; *In re Samour*, 571 F.2d 559, 563-64 [197 USPQ 1] (CCPA 1978). The reason is that section 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." *Hafner*, 410 F.2d at 1405; *see* 1 Donald S. Chisum, *Chisum on Patents* §3.04[1][c] (2002); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-52 [64 USPQ2d 1202] (Fed. Cir. 2001) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method)."

As such, applicant's arguments that the prior art is not enabled is not persuasive. Further, Examples 2-3 of the specification characterisation of pulmonary expression of activin and follistatin in asthmatic tissue, wherein preliminary immunohistochemical analysis reveals loss of follistatin expression in bronchial epithelium after OVA challenge very similar to the pattern seen for activin. It is noted that the `216 publication claims treating asthma, emphysema or

chronic bronchitis using the inhibitor of a Hedgehog signalling pathway such as follistatin (see published claims 7, 26 and 29). Yet, Applicant argues that the reference is not enabled and the public is not in possession of the claimed method. There is no requirement under 102 to reduce to practice in order to anticipate.

The declaration by Dr. David Morritz de Kretser, under 37 CFR 1.132, filed 07/08/2011, is insufficient to overcome the rejection of claims 74-78 as anticipated over US 20020192216 because ¶4-¶6 is silence with respect to the treatment of severe acute respiratory distress syndrome or asthma with hedgehog signaling pathway inhibitor follistatin. The declaration does not even mention the treatment of severe acute respiratory distress syndrome or asthma using the Hedgehog signaling inhibitor follistatin.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claim 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over US20030162715.

The ` 715 publication teaches follistatin-3 protein binds to activin in a dose-dependent manner in the above-described assay (see ¶5, 22, 85), wherein it binds to activin A and B (see ¶560&563). The `715 publication teaches the use of follistatin-3 polypeptides to treat disease. For example, patients can be administered follistatin-3 polypeptides in an effort to replace absent or decreased levels of the follistatin-3 polypeptide, to supplement absent or decreased levels of a different polypeptide, to inhibit the activity of a polypeptide, to activate the activity of a polypeptide, to reduce the activity of a membrane bound receptor by competing with it for free ligand, or to bring about a desired response (see ¶338). The `715 publication further teaches that follistatin-3 polynucleotides or polypeptides cam also be useful in treating autoimmune disorders (see ¶391). Examples of autoimmune disorders that can be treated include, but are not limited to: rheumatoid arthritis or Autoimmune Pulmonary Inflammation (see ¶392). Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by follistatin-3 polynucleotides or polypeptides (see ¶393). The `715 publication

teaches that follistatin-3 polynucleotides or polypeptides, can also be used to modulate inflammation. For example, follistatin-3 polynucleotides or polypeptides can inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.) (see ¶395). The `715 publication teaches a pharmacological composition of the invention use or sale for human administration (see ¶234, 235, 612).

The `715 publication differs from the claimed invention only in the recitation of follistatin in claims 74-78.

However, the `715 teaches we demonstrate that FLRG (follistatin-3) is a functional activin-binding protein which, like follistatin, binds both activin A and activin B. However, we demonstrate differential expression in tissues and regulation of follistatin and FLRG expression in cultured keratinocytes. Our results indicate differences in the in vivo regulation and functions of FLRG and follistatin proteins (see ¶549, ¶560). Further, the family of inhibin-related proteins currently consists of at least four groups of members; inhibins, activins, and two splice variants of follistatin-1 (315 and 288 amino acids) (see ¶3). The ability of FLRG (follistatin-3) to associate with activin A was comparable to FS-315 and FS-288, as judged from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates. These results demonstrate that FLRG, like FS-315 and FS-288, can bind the unprocessed high molecular weight activin A precursor (see ¶563). Judging from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates, the ability of FLRG to co-immunoprecipitate activin B was at least as good as that of FS-315 and possibly even better than that of FS-288 (see ¶565).

Those of skill in the art would have had reason to use the follistatin of the `715 publication as a substitute for the treatment taught in the `715 publication because, like the follistatin-3 taught in `715 publication, follistatin are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 07/08/2011, have been fully considered, but have not been found convincing.

Applicants disagree that follistatin-3 (also known as follistatin related- gene or FLRG) are substitutions for one another. Even the '715 reference teaches that, "we demonstrate that FLRG is a functional activin-binding protein which, like follistatin, binds both activin A and activin B... [h]owever, we demonstrate differential expression in tissues and regulation of follistatin and FLRG expression in cultured keratinocytes... [o]ur results indicate differences in the in vivo regulation and functions of FLRG and follistatin proteins" (the '715 publication at ¶549). Moreover, as stated in the de Kretser Declaration at ~[10, it is known in the art that follistatin-3 and follistatin are encoded by separate genes and, although they do show some homology, each is a unique protein with distinct roles as demonstrated when the gene for each protein is knocked out. As described in the de Kretser Declaration at ¶10, Matzuk, et al. report that knock-out of the follistatin gene results in the death of all offspring within a few hours after birth. In contrast, disruption of the follistatin-3 gene in mice reported by Mukherjee, et al. resulted in mice surviving to adulthood.

However, the knock-out results and the being encoded by separate genes do not prove that follistatin-3 cannot bind the unprocessed high molecular weight activin A precursor and follistatin-3 would not act as activin-binding protein.

In addition, as stated in the de Kretser Declaration at ¶11, although the two proteins have follistatin domains with some homology, follistatin-3 and follistatin share only 61.5% amino acid sequence similarity and 43.25% identity. Importantly, follistatin has a lysine-rich heparin binding sequence in the follistatin domain 1, which enables follistatin to bind to heparin sulfate proteoglycans on cell surfaces, targeting any follistatin-bound activin to a lysosomal degradation pathway. Follistatin-3 has no such site and cannot initiate the degradation of activin after it is bound. Moreover, it has been demonstrated that follistatin-3 is 50-100 fold less potent in neutralizing the effects of endogenously produced activin production than follistatin, whereas follistatin-3 is only 2.4 fold less potent than follistatin in neutralizing the effects of exogenously added activin A. Dr. de Kretser concludes that given that inflammatory disorders involve the production of endogenous activin at one or more sites, the absence of the heparin binding site in follistatin-3 would render it ineffective as a therapeutic in these settings.

Again, sequence homology is irrelevant to the follistatin-3 acts as a functional activin-binding protein, since small organic molecules, small peptides among others can bind to activin irrespective of the sequence homology. It is not clear to the Examiner what is the significant of the degradation pathway in the method of treating severe acute respiratory distress syndrome or asthma. The Examiner notes that the specification discloses that preliminary immunohistochemical analysis reveals loss of follistatin expression in bronchial epithelium after OVA challenge very similar to the pattern seen for activin (see, [0234] and Example 2) in airway epithelium treated with OVA (day 8). That is downregulation of the activin contributes allergic asthma condition. It appears that the declaration supports the Examiner's position that follistatin-3 would be better than follistatin because follistatin-3 cannot initiate the degradation of activin after it is bound. Regarding the issue that follistatin-3 is 50-100 fold less potent in neutralizing the effects of endogenously produced activin production than follistatin. The Examiner notes that claims are not limited to follistatin but also recites follistatin 288 and 315. The `715 teaches that the ability of FLRG (follistatin-3) to associate with activin A was comparable to FS-315 and FS-288, as judged from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates. These results demonstrate that FLRG, like FS-315 and FS-288, can bind the unprocessed high molecular weight activin A precursor (see ¶563). Judging from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates, the ability of FLRG to co-immunoprecipitate activin B was at least as good as that of FS-315 and possibly even better than that of FS-288 (see ¶565). Importantly, it is the examiner's position that any

measurable level in the downregulation/treatment achieved by FLRG is considered to be an improvement in inhibiting the inflammatory response. A known or obvious composition does not patentable simply because it has been described as somewhat inferior to some other product for the same use. See In re Gurley 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See MPEP 2123. There is no discouragement nor skepticism in the prior art for select follistatin among the other follistatins including FLRG.

Applicant further argues that it has been reported in the literature that the effects of follistatin and follistatin-3 on activin A- or BMP2-mediated gene expression are different depending on the target (discussed in the de Kretser Declaration at ¶12); and it has been found in heart failure that follistatin and follistatin-3 have different effects and expression patterns (discussed in the de Kretser Declaration at ¶13). Dr. de Kretser, as one with skill in the art, concludes at ¶14 that the differences between follistatin and follistatin-3 demonstrate that they are not biologically substitutable one for the other particularly in the context of binding activin. Additionally, Dr. de Kretser at ¶15 states that in his review of the literature, he did not find any reported study demonstrating that follistatin-3 is effective in treating inflammation.

The Examiner agrees with Dr. de Dretser that the effects of follistatin and follistatin-3 activin A-mediated gene expression are different depending on the target. While the heart failure is not at issue in the instant case, however, as the declaration states that it is known that follistatin has a lysine-rich heparin binding sequence in the follistatin domain 1, which enables follistatin to bind to heparin sulfate proteoglycans on cell surfaces, targeting any follistatin-bound activin to a lysosomal degradation pathway. Follistatin-3 has no such site and cannot initiate the degradation of activin after it is bound. Contrary to Dr. de Kretser conclusion that follistatin and follistatin-3 are not biologically substitutable one for the other in the context of binding activn, the `715 teaches we demonstrate that FLRG (follistatin-3) is a functional activin-binding protein which, like follistatin, binds both activin A and activin B. The `715 publication teaches the ability of FLRG (follistatin-3) to associate with activin A was comparable to FS-315 and FS-288, as judged from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates. These results demonstrate that FLRG, like FS-315 and FS-288, can bind the unprocessed high molecular weight activin A precursor (see ¶563). Judging from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates, the ability of FLRG to co-immunoprecipitate activin B was at least as good as that of FS-315 and possibly even better than that of FS-288 (see ¶565). Accordingly, those of skill in the art would have had reason to use the follistatin of the `715 publication as a substitute for the treatment taught in the `715 publication because, like the follistatin-3 taught in `715 publication, follistatin are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

Applicant submits that the biological and chemical arts are generally accepted to be unpredictable.. The Federal Circuit confirmed this in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353 (Fed. Cir. 2008), stating, "[t]o the extent an art is unpredictable, as chemical arts often are, KSR's focus on...'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." Id. at 1359. Applicants argue that this is particularly true when talking about proteins that are as different as follistatin and follistatin-3, as seen in the vastly different results in knock-out models of these proteins.

Applicant's generalized assertions of unpredictability in substituting follistatin with follistatin-3 protein in a method of treatment are inconsistent with the instant disclosure as filed [0126], which describes antagonists may be any compound capable of blocking, inhibiting or otherwise preventing activin from carrying out its normal biological function. Antagonists include monoclonal antibodies and antisense nucleic acids which prevent transcription or translation of activin genes or mRNA in mammalian cells. Modulation of expression may also be achieved utilising antigens, RNA, ribosomes, DNAzymes, aptamers, antibodies or molecules suitable for use in cosuppression. Suitable antisense oligonucleotide sequences (single stranded DNA fragments) of activin may be created or identified by their ability to suppress the expression of activin [0126]. There is no evidence that these agents, follistatin with follistatin-3, behave any differently or produce results that are different from the other activin antagonists listed in the specification.

Applicant further argues that the `715 publication fails to exemplify even one therapeutic indication that can be treated with follistatin-3. Nevertheless, the `715 publication recites that follistatin-3 may be useful in the treatment a laundry list of diseases listed at ¶¶392-440. Applicant contends that "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, MS*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Applicants submit that the '715 publication like the '216 publication simply tosses out the mere germ of an idea to use follistatin-3 to treat a voluminous array of human diseases and disorders without one single example or exemplification of success using follistatin-3 to do so. Thus, Applicants respectfully submit that one skilled in the art would have had to perform an undue amount of experimentation to decipher which, if any, of the therapeutic indications recited in the '715 publication are indeed treatable by follistatin-3--much less follistatin--particularly given the unpredictable nature of the biological arts and the biological differences between follistatin and follistatin-3.

However, in instant specification, like the `715 publication, there are no working examples. The use of follistatin to treat severe acute respiratory distress syndrome or asthma to realize a therapeutic effect on the "aberrant, unwanted or otherwise inappropriate inflammatory response" is only a theory. There is no evidence of record that demonstrates that it is the antagonism of activin A that produces the therapeutic effects of inflammatory response in sever acute respiratory distress syndrome or asthma. The teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is placed on applicant to point out how the teachings of the specification go beyond those of the prior art.

15. Claims 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20020192216 as is evidenced by van Eyll et al (Jounal of Cell Science 117(10):2077-2086, 2003) or WO 8911862, each in view of WO/ 2003/006057.

The teachings of 216 publication and van Eyll et al have been discussed, supra.

The `216 differs from the claimed invention in the recitation of follistatin 288 or follistatin 315 in claims 76-77.

The `057 publication teaches that the activin antagonist is follistatin, or a fragment(s) or analogue thereof, and more typically the follistatin is a single chain protein comprising between 288 and 315 amino acids (see page 4, lines 16-19).

Those of skill in the art would have had reason to use the follistatin 288/315 of the '057 publication as a substitute for the treatment taught in the '216 publication because, like the compounds taught in `216 publication, follistatin 288/315 are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. The Declaration of Dr. David Morritz de Kretser, filed 07/08/2011, is insufficient to overcome the rejections under art for the reason set forth above.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 16, 2011

/Maher M. Haddad/
Primary Examiner, Art Unit 1644